REMARKS

In the Office Action dated January 10, 2008, claims 39-56 are pending and under consideration. Claims 39-56 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 39-56 are also rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to satisfy the enablement requirement. The application is also objected to for allegedly containing sequences that are not indentified by sequence identifiers.

This Response addresses each of the Examiner's rejections and objections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

Objection Relating to Sequences

In the Action, the Examiner has objected to the application for containing sequences that are not indentified by sequence identifiers. Specifically, the Examiner states that the specification references a *T. reesei* α-1,2-mannosidase and an OCH1 gene without corresponding sequence identifiers.

With respect to the OCH1 gene, the Examiner's attention is directed to the specification at page 26, lines 5-9. Applicants have further amended this paragraph to clarify that the nucleotide sequence of the *Pichia pastoris* OCH1 gene is set forth in SEQ ID NO: 2, which encodes a protein having the amino acid sequence of SEQ ID NO: 3. The amendment to the specification is also supported by the application as originally filed (e.g., pages 35-36).

Regarding *T. reesei* α-1,2-mannosidase, the specification describes that a preferred enzyme is the one described by Maras et al., *J. Biotechnol.* 77: 255-63 (2000). A copy of this

reference is provided herewith as **Exhibit 1**. The amino acid sequence of the enzyme is set forth in Figure 1 of the reference. Although the *T. reesei* α-1,2-mannosidase sequence is not explicitly provided in the present application, the *T. reesei* α–1,2-mannosidase gene and protein sequences are both available in GenBank (under Accession No. AF212153 and AAF34579, respectively). Further, the open reading frame of the expression vector pGAPZMFManHDEL is set forth in SEQ ID NO: 8, and encodes a fusion protein composed of the prepro-signal sequence of the *S. cerevisiae* α-mating factor, *Trichoderma reesei* α-1,2-mannosidase cloned in frame with the signal sequence, and the ER localization signal "HDEL". See also Figure 3B and page 26, line 25 to page 27, line 4 of the specification for the description of pGlycoSwitchM5. To clarify, the paragraph beginning on page 26, line 25 has been amended to insert a reference to SEQ ID NO: 8. Support for such amendment is found in the application as originally filed, for example, on page 37 in reference to SEQ ID NO: 8 (as setting forth the ORF of the MFManHDEL fusion in pGAPZMFManHDEL). No new matter is introduced.

In view of the foregoing, the Examiner's objection to the specification for allegedly failing to comply with the sequence rules is overcome. Withdrawal of the objection is therefore respectfully requested.

35 U.S.C. §112, first paragraph (written description)

Claims 39-56 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner contends that the claims are directed to a genus of genetically engineered methylotrophic strains containing a disruption of its genomic OCH1 gene, including *Candida*, *Hansenula*, *Toulopsis* and *Pichia*, which strains express *T. reesei* α-1,2- mannosidase or a functional part thereof, and any GalT or a functional part thereof,

and any GnT1 or a functional part thereof. The Examiner is of the opinion that the limited number of species disclosed in the specification is not representative of the genus as claimed, and therefore the claimed subject matter is not adequately described in the specification as required by the written description requirement.

In the first instance, Applicants respectfully direct the Examiner's attention to the fact that independent claim 39 has been amended to define the strain as a *Pichia* strain. In this context, Applicants take note of the fact that the strain formerly known as *Hansenula polymorpha* has been reclassified and renamed as *Pichia angusta*, and is therefore also a strain of *Pichia*. Applicants respectfully submit that the disclosure of the disruption of the OCH1 gene in *Pichia pastoris* is certainly representative of the OCH1 gene from a *Pichia* strain. Therefore, in light of the amendments to the claims to further define the methylotrophic strain as a *Pichia* strain, and given the exemplification of OCH1 disruption in *Pichia pastoris*, the claimed subject matter insofar as the strain and its OCH1 disruption are concerned is adequately described in compliance with the written description requirement.

Turing to *T. reesei* α-1,2- mannosidase or a functional part thereof, the Examiner contends that no teaching regarding the structure or a correlation between structure and function of this enzyme is provided in the specification other than a general reference to the prior art.

In response, Applicants respectfully submit that *T. reesei* α-1,2- mannosidase was already an enzyme well characterized in the art at the time the present application was filed, and therefore fragments of this enzyme that are expected to substantially retain the functional activity of the enzyme, such as its catalytic domain, were already described in the art or could be readily determined by those skilled in the art. As support of this position, Applicants provide herewith **Exhibit 2**, which provides an alignment of amino acid sequences of several α-mannosidases

(including *T. reesei* α-1,2- mannosidase), all of which were available at the time the present application was filed. Such sequence alignment reveals very clear homology, which permits an easy determination of the conserved catalytic domains of these proteins (shown by shaded area). Furthermore, these mannosidases (including *T. reesei* α-1,2- mannosidase) are members of a conserved family referred to as class I mannosidases, which also includes murine α-1,2-mannosidase. See Maras et al. (**Exhibit 1**), page 259, left column, and Figure 1. Notably, a fragment of murine α-1,2- mannosidase containing its catalytic domain was also described in WO02/00856 (**Exhibit 3**), which, upon expression in *Pichia pastoris*, reduced the number of α-1,2-mannoses present on the N-glycans. See the table on page 32, bridging paragraph of pages 33-34, and lines 14-17 on page 42 of WO02/00856 (**Exhibit 3**). All these documents simply support Applicants' position that functional parts of *T. reesei* α-1,2- mannosidase fragments that are expected to substantially retain the functional activity of the enzyme, such as its catalytic domain, could be readily determined or envisioned by those skilled in the art at the time the present application was filed. Therefore, functional parts of *T. reesei* α-1,2- mannosidase and use thereof in the context of the present invention are adequately described in a manner that satisfies the written description requirement.

Similarly, for GnTI, a range of sequences from a multitude of organisms was available at the time of filing and could easily be retrieved from Genbank. Sequence alignment of several GnT1 proteins (**Exhibit 4**) easily reveals where the catalytic domains are approximately located: they are the regions that are most conserved even in very distantly related organisms. Moreover, the programs Coils and Paircoil, both available at the time the present application was filed and accessible via the www.expasy.ch website would, allow the identification of a "coiled coil" domain between the hydrophobic membrane anchor (which can

also be easily identified using softwares such as ss TMpred, also at www.expasy.ch) and the conserved catalytic domains in several of the sequences. The coiled coil domain is indicated as underlined for the murine sequence in **Exhibit 4**. Such coiled coils are known and well-studied protein oligomerization domains and are not involved in catalysis. Those skilled in the art would also easily note the proline-rich stretches before and after the predicted coiled coil domain (indicated for the murine sequence by lower cases in **Exhibit 4**). Proline breaks regular secondary structure and is often found in stretches between functional elements of a protein ("spacer").

As for β 1,4-galactosyltransferases (GalT), again multiple sequences were documented in the art at the time the present application was filed and could be easily retrieved from Genbank. **Exhibit 5** provides alignment of several GalT proteins from phylogenetically very diverse organisms. Yet the catalytic domain of the proteins is very identifiably conserved, as can be observed from the sequence alignment in **Exhibit 5** (homology starting at residue 131 of the murine sequence).

Therefore, for both GnT1 and GalT, the art documented, at the time the present application was filed, sequences from multiple species available for use in the present invention, and the catalytic domains of the proteins could be readily determined based on a routine sequence alignment. Applicants respectfully submit that what is conventional or well known to one skilled in the art need not be disclosed in detail. See Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986); Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991); Martin v. Johnson, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972). Accordingly, the description of GnT1, GalT and functional parts thereof in the specification is adequate and in compliance with the written description

requirement.

Applicants have also added claims 57-59 to further define the functional parts of the enzymes as comprising the catalytic domain of the respective enzymes. Support for these new claims is found in the specification, e.g., page 11, lines 10-26; page 14, lines 18-21; and page 16, lines 8-11.

In view of the foregoing, the written description rejection under 35 U.S.C. §112, first paragraph is overcome and withdrawal thereof is respectfully requested.

35 U.S.C. §112, first paragraph (enablement)

Claims 39-56 are rejected under 35 U.S.C. §112, first paragraph, for lacking enablement. The Examiner contends that the specification does not provide enablement for all the claimed methylotrophic yeast strains wherein the endogenous OCH1 gene was identified and disrupted, and which further express *T. reesei* α-1,2- mannosidase or a functional part thereof, and any GalT or a functional part thereof, and any GnT1 or a functional part thereof. In particular, the Examiner states that the specification does not teach how to identify OCH1 genes from sources other than *Pichia pastoris* and provides no guidance regarding the similarities between the OCH1 genes from different sources.

Applicants again respectfully direct the Examiner's attention to the fact that independent claim 39 has been amended to define the strain as a *Pichia* strain. It is noted that the cloning of the *Pichia pastoris* OCH1 gene, as disclosed in Japanese patent application 07145005 (referenced on page 26, line 5-7 of the specification), was based upon prior knowledge of the sequence of the *S. cerevisiae* homolog. As understood by one skilled in the art, divergence between *S. cerevisiae* and *P. pastoris* is larger than between *P. pastoris* to other *Pichia* species

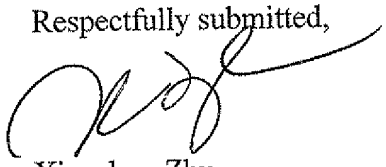
including, e.g. *Pichia methanolica*, *Pichia angusta* (formerly *Hansenula polymorpha*), *Pichia stipitis*, *Pichia anomala*. Thus, in light of the fact that one of ordinary skill in the art was able to clone the OCH1 gene of *P. pastoris* based on the knowledge of the *S. cerevisiae* OCH1 homolog sequence, one skilled in the art would have been able to clone OCH1 genes from other *Pichia* species based on the *P. pastoris* OCH1 sequence, without undue experimentation. As evidence that cloning of other OCH1 genes would not be undue, Applicants submit that the OCH1 genes from *P. stipitis* and *Pichia angusta* have been isolated subsequent to the filing of the present application and are now available in Genbank under Accession No. XP_001383155 and AAS77488.1, respectively.

By aligning the OCH1 sequences of *S. cerevisiae*, *Pichia angusta*, *Pichia stipitis* and *Pichia pastoris* (**Exhibit 6**), it can be seen that clear similarities are found between the 3 *Pichia* sequences, but that these *Pichia* sequences as a group are quite different in a number of locations from the *S. cerevisiae* sequence (in particular, the *Pichia* sequences have deletions of varying length in common in places, which are not found in the *S. cerevisiae* sequence).

In sum, in light of the teaching provided in the specification, those skilled in the art would be able to identify OCH1 genes from other *Pichia* species, without undue experimentation. Further, as discussed above, both the specification and the art provide ample guidance for *T. reesei* α-1,2- mannosidase, GnT1, GalT and functional parts thereof. Accordingly, those skilled in the art would be able to make the strains as claimed, without undue experimentation. Reconsideration and withdrawal of the enablement rejection under 35 U.S.C. §112, first paragraph, are respectfully requested.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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